SUMMARY OF SAFETY AND EFFECTIVENESS DATA

GENERAL INFORMATION

Device Generic Name:	Implanted Infusion Pump
Device Trade Name:	Medtronic® SynchroMed™ Infusion System
Applicant's Name and Address:	Medtronic, Inc. 3055 Old Highway Eight P.O. Box 1453 Minneapolis, Minnesota 55440
Premarket Approval Application (PMA) Number:	P860004
Date of Panel Recommendation:	November 3, 1986
Date of Notice of Approval to the Applicant:	MAR 14 1988

I. INDICATIONS FOR USE

The Medtronic® SynchroMed™ Infusion System, hereinafter referred to as Infusion System, is an implantable, programmable, drug delivery system which may be used in patient therapy for the chronic intravascular infusion of floxuridine (FUDR) or doxorubicin hydrochloride (Adriamycin) and, when required, bacteriostatic water, physiological saline (0.9 percent (%) sodium chloride, U.S.P.) and/or heparin.

Background

The regional intraarterial infusion of FUDR is used in the palliative management of unresectable, solid tumors of the liver or colon. The systemic intravenous infusion of Adriamycin is used in the palliative management of various solid tumors, lymphomas and leukemias. Bacteriostatic water or physiological saline is used to achieve the desired concentration of FUDR or Adriamycin and to flush the drug reservoir. Heparinized physiological saline may be used during an interruption in FUDR therapy to maintain catheter patency. However, such action does not apply to Adriamycin because it is not compatible with heparin.

II. DEVICE DESCRIPTION

The implantable components of the system include the Models 8610H and 8611H SynchroMed™ Pumps, the Models 8700, 8702 and 8710 Vascular Catheters, the Model 8500 Access Port, the Models 8500-1 and 8500-10 Port Connectors, the Model 8800 Physician Programmer (Programmer), and a variety of catheter accessories.

Both SynchroMed™ pump models are implantable battery-powered pumps that store and dispense drugs in accordance with information transmitted from the Programmer. Each SynchroMed™ pump contains a self-sealing septum, a collapsible 18 milliliter (ml) drug reservoir, a peristaltic pump, motor, microprocessor-based control circuitry, and a lithium thionylchloride battery. The Model 8611H pump differs from the 8610H pump only in that the former model contains a 0.22 micrometer pore size bioretentive filter in the reservoir fluid outlet. The Model 8610H pump is available as a result of a preliminary marketing survey conducted by the applicant. Many physicians did not believe that a filter was necessary for the delivery of chemotherapeutic agents. The selection is based upon each physician's preference. Further reference to a SynchroMed™ pump in this section applies to both Model 8610H and Model 8611H.

The drug reservoir is a sealed titanium chamber which can be filled or evacuated using a syringe and hypodermic needle to percutaneously puncture its self-sealing septum. A rotary peristaltic pump dispenses the drug from the reservoir with an accuracy of plus or minus (+) 15%. However, because of the various errors that may occur during the filling and emptying of the reservoir, the observed volume delivered by the pump may vary by ± 25% with respect to the expected value. The peristaltic pump functions by moving a rotor through a circular case pushing fluid through a tube. The rotor, driven by a step motor through a gear train, controls the delivery rate of the fluid. The step motor is controlled by microprocessor-based electronics,

which is noninvasively programmed via specific radiofrequency signals generated by the Programmer. With the programming wand positioned over the implanted device to provide the magnetic field, the radiofrequency signals are transmitted from the antenna in the wand to the antenna in the SynchroMed™ pump.

The SynchroMed™ pump's programmed data include patient identification, date, current prescription, drug name, concentration, dose rate, infusion mode, reservoir volume and the alarm status. The Programmer can be used to switch the pump on or off or to select one of five infusion modes.

The SynchroMed™ pump has an audible alarm system which warns the patient or physician of low battery power, low reservoir volume or a pump memory error. This alarm system is especially helpful to patients who live in their homes on an outpatient basis.

The SynchroMed™ pump battery is a single lithium thionylchloride cell with a nominal rating of 3.65 volts. Its longevity, related to the programmed rate of delivery, is 3 years at a dispense rate of 1.5 ml per day (ml/day).

The reservoir volume and the low reservoir volume alarm indicator are programmed in the SynchroMed™ pump. As the SynchroMed™ pump dispenses fluid, it calculates and monitors the remaining reservoir volume. When the volume dispensed matches the programmed low reservoir level, the pump activates the low reservoir alarm.

Finally, if erroneous data is detected in the memory, the infusion cycle in process is stopped, and the pump memory error alarm is activated.

Three radiopaque catheters are intended for intravenous (IV) or intraarterial use with the SynchroMed™ pump. The Model 8700 Catheter, 6.5 French size with a 0.040 inch diameter lumen, has attached anchoring rings and can be trimmed to length to facilitate the surgical procedure. The Model 8700 Catheter is indicated for intravenous or intraarterial use. The Model 8702 Catheter, similar but intended for small arterial access, has a 4 French size with a 0.012 inch diameter lumen. The Model 8710 Catheter uses a trilaminate structure with metal coil reinforcement laminated between inner and outer layers of silicone tubing. The inner and outer silicone tubes are sealed to each other at the proximal and distal ends so that the metal coil does not contact drug, tissue or blood. Its size is 4 French with a 0.012 inch diameter lumen. Several models with different lengths and anchoring ring options are available. The Model 8710 Catheter is indicated for intravenous use.

The Infusion System may be implanted with, or without, an Access Port. The Port Connector Assemblies, used to connect the SynchroMed™ pump, Access Port and Model 8700, 8702, or 8710 Catheter, allow infusions from both the SynchroMed™ pump and the Access Port. An in-line valve directs fluid from the Access Port into the selected catheter but inhibits flow from the Access Port to the SynchroMed™ pump.

III. ALTERNATIVE PRACTICES AND PROCEDURES

FUDR may be administered by continuous intraarterial infusion via a catheter

inserted into the arterial blood supply of the tumor. An external or implantable infusion pump may be used to overcome pressure in large arteries.

Adriamycin may also be administered intravenously by direct injection using a syringe and hypodermic needle or into a freely running IV infusion, i.e., an IV drip or an external pump. To facilitate access to a large vein, Adriamycin may be administered using an external or implantable, indwelling catheter.

IV. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Infusion System related complications may decrease, increase or stop the delivery of medication. Extravasation of FUDR or Adriamycin may cause severe tissue necrosis. Infection and erosion of the device through the skin may also occur.

Potential adverse effects associated with implantable, programmable devices may be caused by battery or other component failure, programmer failure and the presence of uncommon and intense electromagnetic interference.

Potential adverse effects associated with all implanted catheters may be caused by partial or complete occlusion, angulation, migration or dislodgment, vessel thrombosis and failure to comply with proper implant procedures. Surgical intervention may be necessary to restore proper system function.

V. CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

The SynchroMed™ pump is contraindicated when it cannot be implanted less than 2.5 centimeters (cm) from the surface of the skin and/or when the patient has an implanted programmable medical device. Drug labeling dictates the contraindications associated with the use of FUDR, Adriamycin, physiological saline, bacteriostatic water or heparin. See attached labeling for warnings and precautions (Attachment A).

The device should not be implanted in the presence of infection.

Patients whose body size is not sufficient to accept the pump bulk and weight are not suitable candidates.

VI. SUMMARY OF STUDIES

A. In Vitro Studies

In vitro studies included the testing of the device components, SynchroMed™ Programmer interface and the finished device. Most of the testing was conducted using pumps in a chamber maintained at 37°C and 95 to 100% relative humidity; the remainder was conducted at ordinary room conditions.

Of all components, the battery bench testing demonstrated the shortest life span, 3 years, based upon a typical clinical regimen of 1.5 ml/day (for a total delivery of 1642 ml over 3 years). Consequently, longevity testing was compared to either 1642 ml of delivery or 3 years duration to determine acceptability. The battery is discussed later in the summary.

Pump Assembly

Longevity testing was comprised of 34 pump assemblies pumping sterile water until failure. Total volumes dispensed ranged from 4974 ml to 9126 ml with 7983 ml as an average for the 34 pumps. Since the typical clinical regimen for cancer chemotherapy requires the delivery of approximately 1.5 ml/day (1642 ml over three years), the accelerated test results (see test No. 3 below) show that the pump assembly will last at least 9 years.

Two pumps were each used to dispense FUDR and Adriamycin (approximately 700 ml), with a simulated arterial pressure of 260 millimeters of mercury (mmHg), for a minimum of 40 refill cycles. Flow rates varied from 0.216 to 21.6 ml/day. The results indicate that the dispensed volume per revolution was within $\pm$ 4% of the expected value.

The following tests were conducted to determine the effect of various parameters on the accuracy of the pump:

1. The reservoir pressure was varied from -1 to +9 pounds per square inch gauge (psig). (The nominal reservoir pressure is +5 psig.)

2. The pressure at the outlet port of the pump assembly was varied from -3 to +3 psig.

3. The speed of the pump's rotor was varied to deliver between 0.9 and 28.8 ml/day.

The results of these tests demonstrated that the flow delivered by the pump remained within $\pm$ 15% of the expected value.

Reservoir

The SynchroMed™ reservoir consists of a multiconvoluted titanium bellows pressurized by a volatile liquid that surrounds the outside of the bellows. Three reservoirs were fatigue tested to verify reliable function over the life of the Infusion System. Five reservoirs were injected with cold (1°C) fluids. Positive reservoir pressure was achieved in less than 2.5 minutes. Pump accuracy will not be significantly affected. Extreme positive (30 psig) and negative (-10 psig) internal pressures were developed for a period of 24 hours in two devices. Smooth pressure profiles were observed over the anticipated range of reservoir volumes. It is expected that the reservoir will function as specified over the Infusion System's longevity.

Septum

The objective of the septum testing was to assess the reliability of the pump septum and to evaluate its characteristics following exposure to extreme environmental stresses. It is expected that the SynchroMed™ septum will be punctured approximately 90 times under the anticipated clinical conditions.

Sixty-five septums were punctured at least 500 times with a 22 gauge standard bevel needle and all reliably resealed. Ten septums were exposed to 100°C Ringer's solution for 7 days, eight were exposed to 37°C pseudoextracellular fluid for 7 days, and 12 septums were exposed to steam sterilization (250°F).

Loss of sealing characteristics were not observed. Twelve septums were immersed in solvents, such as deionized water, Freon, and isopropyl alcohol for 2 hours without effect on the resealing characteristics.

Filter

Six filter assemblies passed a "bubble point" test prior to and following exposure to environmental stresses such as temperature cycling, vibration and mechanical shock. Five filter assemblies were subjected to short term (7 days) and two were subjected to long term (7 months) microbial challenges. Filtrate samples remained sterile in both cases.

Reed Switch

The reed switch is a small, hermetically sealed vessel containing metal blades (switch contacts) in close proximity that close in the presence of a strong magnetic field. With the reed switch in series with the antenna, the receiver of the hybrid circuit will be able to sense transmissions only when the reed switch is closed.

The reed switch that is used in the Infusion System is identical to those of the commercially available Spectrax and Xyrel cardiac pulse generators. These generators have a combined device experience base of four million months, during which time no reports of adverse performance due to reed switch activation by environmental magnets have been reported.

Battery

Battery longevity was calculated using the battery capacity values obtained from electrical discharge testing and device current drains at various dispense rates. A typical clinical regimen for FUDR or Adriamycin requires an average flow rate of 1.5 ml/day. The average flow rate utilized during the clinical trial was approximately 0.9 ml/day. Based upon a flow rate of 1.5 ml/day, the battery will remain functional following 3 years of service.

The shelf life of each SynchroMed™ pump, solely determined by its integral battery, is displayed on every package label as a "Use Before Date". Under the worst circumstances, an actual shelf storage of 12 months will still permit the pump to deliver 1.5 ml/day for 3 years.

Two hundred twenty-five batteries were discharged at six rates at 37°C. Voltage profiles were smooth in all cases. Sixteen batteries were subjected to mechanical shock and vibration, and high and low temperatures which exceed stress conditions expected during normal use. Open and load circuit voltages, and impedance did not change significantly and discharge curves were nearly identical to controls.

Electronic Hybrid Module

The manufacturing of the electronic hybrid module uses the same process and technologies used in most Medtronic cardiovascular implantable devices. The major components of the module are the microprocessor, analog interface and interconnect substrate. Among its functions are generation of a sequential data transmission link into and out of the SynchroMed™ pump, monitoring of

battery potential, and a "watchdog" control to assure proper microprocessor function.

Seventy-six microprocessors, life stress tested per Mil-Std-83, presented no failures. Seventy-five analog interface units were subjected to accelerated life tests at 125°C at higher than normal operating voltages. After 1000 hours of life test, there was no indication of drift or other unacceptable performance. Twenty-two microprocessors, subjected to thermal and mechanical stresses per Mil-Std-883, performed acceptably. In addition, during the course of clinical trials, there has not been a complication related to the electronic hybrid module.

SynchroMed™ Pump Hermetic Containment Testing

The Model 8610H/8611H SynchroMed™ pump uses an inner shield which hermetically separates the peristaltic pump and fluid pathway from the hybrid control and battery. Hermetic containment testing on four units verified that hermeticity was obtained and that it could be maintained after exposure to extreme environmental stresses.

SynchroMed™ Pump Accuracy Testing

Four pumps, subjected to mechanical shock, vibration, and thermal shock tests, dispensed fluid within ± 10% of the expected volume. One pump was tested through two six-step complex infusion cycles delivering from 0.06 to 1.2 ml/hr. Both total cycles lasted 11 hours (hrs) and the entire test lasted 22 hrs. The pump dispensed fluid within the ± 10% of the expected volume. Three pumps were each tested through a 24 hr seven-step complex bolus infusion with flow rates from 0.013 to 1.2 ml/hr. Again, dispensed fluid was within ± 10% of the expected volume. Five pumps were tested with back pressures of up to +12 psig applied at the outlet port to simulate arterial pressure. Typical arterial pressure is 120 mmHg and, with a back pressure of 6 psig (324 mmHg), the dispensed fluid was within ± 10% of the expected volume. Three pumps were tested with pressures from 0 to -7 psig (17,000 feet (ft) altitude) at the outlet port to simulate different elevations. With fluid delivery rates of 0.06 and 1.2 ml/hr, the pumps dispensed fluid within ± 10% of the expected volume up to -2 psig (4,000 ft. elevation). After one day for pressure equilibration, the volume dispensed was within ± 10% of nominal at -5 psig (11,000 ft. elevation). Four pumps were tested at ambient temperatures from 35°C to 42°C. The dispensed fluid was within ± 10% of the expected volume. Finally, nine pumps were tested for delivery at flow rates similar to clinical conditions. After 43 refill cycles, the dispensed fluid was within ± 10% of the expected volume.

SynchroMed™ Pump Software Testing

The SynchroMed™ pump software, built into the microprocessor read only memory (ROM) during its manufacturing cycle, controls all operations of the SynchroMed™ pump. Tests conducted on the software included all alarm functions, proper motor pulse widths, properly functioning telemetry, delivery of three different continuous flow rates, delivery of a complex bolus, stopping pump operation, and response to a watch-dog (control that guarantees continued microprocessor self-test) timer interrupt. The SynchroMed™ pump software correctly performed the programmed operations.

Only components that pass the test sequence are assembled into the completed product.

Two devices have been tested to ensure that the software operates the pump according to parameters stored in memory, communicates via radiofrequency telemetry with a programmer to alter the control parameters, and monitors the SynchroMed™ pump's operation to detect abnormal conditions. Each step was performed as expected and no unexpected results were obtained. In addition, no complications related to software were reported during the clinical trials.

SynchroMed™ Pump Environmental Stress Testing

Four SynchroMed™ pumps were subjected to vibration testing, mechanical shock, temperature shock, and extreme temperature storage testing. No significant changes in programmability or dispense characteristics were observed. Electromagnetic Compatibility (EMC) testing was conducted on three pumps according to the Association for the Advancement of Medical Instrumentation (AAMI) Pacemaker Standard. Following simulated exposure to radio, television, radar, microwave ovens, Citizen Band and Mobile radio, airport metal detectors, power lines, defibrillator currents and electrocautery currents, no significant changes in pump motor speed were observed.

SynchroMed™ Pump Longevity Testing

The components and subassemblies that comprise the SynchroMed™ pump were tested to determine longevity and to verify acceptable performance.

The SynchroMed™ pump longevity is based upon the component exhibiting the least longevity. The battery exhibits the least longevity of all SynchroMed™ pump components, being 3 years at a programmed dispense rate of 1.5 ml/day.

Other functional components of the SynchroMed™ pump which may affect longevity are the pump assembly, septum, electronic hybrid module and the reservoir. Each of these component test results indicated a lifespan that exceeds 3 years. See the appropriate sections in this summary for further information.

SynchroMed™ Pump/Programmer Programming Interface Testing

The Programmer programmed the SynchroMed™ pump to dispense fluid in all programmable modes of delivery. There were no undetected telemetry errors.

Electromagnetic compatibility testing was conducted to determine system performance under the influence of various electromagnetic interference (EMI) conditions (reference FDA Medical Device Publication, MDS-201-0004, "Electromagnetic Compatibility Standard for Medical Devices"). The Programmer/SynchroMed™ pump telemetry link performed satisfactorily during exposure to a wide range of frequencies and amplitudes of EMI.

Model 8800 Physicians Programmer Testing

The Programmer was functionally tested to determine if it properly operates

through the menu following selection of expected and unexpected keystrokes. Every path within the software menu structure was tested to verify that each path was available and could be entered and exited using the indicated keystrokes. An attempt was made to enter out-of-range variables. Thermal, electrical and mechanical environmental testing was performed to assess programmer reliability. Functional testing was conducted before and after each of the environmental tests to assure adequate performance.

The Programmer correctly programmed and interrogated the SynchroMed™ pump and remained functional following exposure to environmental stresses beyond those during normal conditions of use.

Vascular Catheter Testing

The three vascular catheters used with the SynchroMed™ pump have been commercially available since November 6, 1985. For the PMA application, mechanical testing was conducted to assess leak resistance, burst strength, pressure/flow characteristics, bond pull strength, connector-to-port pull strength and guidewire insertion. No failures were observed following exposure to thermal shock, pseudoextracellular fluid (PEF), Ringer's solution and adverse flexure conditions.

A brief summary of catheter tests is shown in the following table. All catheter test specimens passed the tests.

Type of Test	Catheter Model Tested	Test Quantities
Burst Strength	8700	3
	8702	2
	8710	6
Leak Resistance	8700	11
	8702	6
	8710	12
Kink Resistance (Pressure Flow Characteristics)	8700	2
	8702	6
	8710	8
Connector Tubing Bond Strength	8700	2
	8702	3
	8710	4
Anchoring Ring to Tubing Bond Strength	8700	4
	8702 (Small Ring)	3
	8702 (Large Ring)	3
	8710	16
Connector to Port Pull Strength	(Same Geometry)	15
Guide Wire Insertion/ Withdrawal	8700	6

Thermal Shock (followed by Bond/Pull Test)	8710	7
PEF (followed by Bond/ Pull Test)	8700	7
100°C Ringers Solution	8702	3
	8710	3
Flex Test	8710	11

One hundred seventy-six catheters have been implanted for a total of 1,111 months of experience. No complications related to catheter failure were reported.

Access Port Testing

The Model 8500 Access Port has been commercially available since November 6, 1985.

Forty-nine Access Ports were leak tested at 80 psig (helium). One failure at less than 5 psig was observed. Since fluid containment is critical to device function, all units are inspected in production. Eight Access Ports were punctured with a standard bevel 22 gauge needle or a Huber point 22 gauge needle. After 450 punctures, leak testing at 30 psig showed all Access Ports to be free of failure. Typical arterial applications incur 3 psig. Five Access Ports were subjected to common hospital cleaning solutions, i.e., deionized water, Freon TF, Freon TMS, Freon TE, and isopropanol, to determine the effect on the material. No significant weight or dimensional changes were observed. Twenty-six units were boiled in Ringer's solution for 7 days with no observation of failure.

Port Connector Testing

Thirty-three Port Connector assemblies were tested. The inlet valve may stick, according to pressure flow tests. But, gentle squeezing, indicated in the technical manuals, will easily open the valves. Inlet valves have not been observed to stick closed after implantation. Severely deformed configurations can prevent fluid flow. Four configurations including twisting the Access Port tubing or pump tubing 235°, squeezing the "T" or kinking the "T" cause a squeezing of the valves. But, the model geometry makes these configurations highly unlikely.

Three hundred forty-five Port Connector assemblies were exposed to Ringer's solution at 100°C for 5 days. Ninety units passed the leak test, 69 passed the pressure burst test, 22 passed the pressure flow characteristics test, 149 passed the bond pull strength test, and 15 passed the connect pull strength test for a total of 345 assemblies tested. No assembly failed any of these tests.

Port Connector flushing characteristics were observed following blood withdrawal using animal blood or a solution of polyethylene glycol mixed with red dye and water. Twenty Port Connectors were observed (10 Model 8500-1 and

10 Model 8500-3). All were filled with either blood or the test solution and water or saline and were flushed through the Port Connector at a rate of 10 ml/minute. An average of 21 ml of saline was required to flush the Model 8500-3 and 1.1 ml for the Model 8500-1. Three units of 22 demonstrated sticky valves that were easily opened with gentle squeezing. All 22 Port Connectors were acceptable. Catheter flushing is addressed together with Port Connector valve sticking in the Technical Manuals.

Compatibility Testing

Drug Stability

Drug stability was determined for the following infusion path materials: titanium, silicone elastomer (septum, catheter tubing, pump tubing, molded elastomer), and fluoropolymer (Access Port Body polymer, membrane filter). FUDR, Adriamycin, and heparin were incubated at 37°C with the individual components of the SynchroMed™ Infusion System for 16 week periods. Stability testing was performed following 1, 2, 4, 8 and 16 weeks of exposure using Ultraviolet-visual (UV-VIS) spectrophotometry and high performance liquid chromatography. Drug stability was assessed based upon a comparison of incubated unexposed drug solutions and material exposed drug solutions to a freshly prepared standard. In accordance with draft FDA guidelines for stability studies (Draft Guidelines for Stability Studies for Human Drugs and Biologics, March 1984, 84D-0115) the lower confidence bound of acceptable stability was defined as greater than or equal to ($\geq$) 90%. FUDR and heparin stability remained $\geq$ 90% for 16 weeks and Adriamycin stability remained $\geq$ 90% for 2 weeks when compared to freshly prepared standards.

To evaluate drug stability during simulated clinical regimens, drug solutions were instilled into 8 SynchroMed™ pumps and dispensed through vascular catheters. The drug stability test data indicate that FUDR (3 SynchroMed™ pumps) and heparin (2 SynchroMed™ pumps) will remain stable (>90%) in the SynchroMed™ pump for a period of 28 days. Adriamycin (3 SynchroMed™ pumps) will remain stable (>90%) for a period of 14 days.

In vivo drug stability studies were conducted and are discussed later in this summary.

Material Compatibility

Samples of materials from the silicone septum, titanium reservoir, filter medium, silicone elastomeric tubing and the fluoropolymeric Access Port body were incubated in drug samples of FUDR and Adriamycin, and heparin and saline at 37°C for periods of up to 16 weeks. The physical properties of these materials were not adversely affected after 16 weeks of incubation in the above fluids.

Biocompatibility

Each material that contacts body tissue directly, or indirectly through the infusion path, underwent in vitro biocompatibility qualification testing, including static hemolysis assay, cell culture agar overlay and mutagenicity testing. These tests were conducted in part under USP Class V, modified, Medtronic standards, and commonly recognized and accepted industrial

standards.

The materials tested were determined to be nonhemolytic, biocompatible and nonmutagenic.

B. Animal Studies

The design and function of the SynchroMed™ Infusion System was tested in vivo. The studies included: biocompatibility testing, acute evaluation of venous and arterial catheters, chronic evaluation of venous catheters, chronic evaluation of SynchroMed™ Infusion System performance when used to infuse the drugs indicated for use, and in vivo drug stability testing.

Each material that contacts body tissue directly or indirectly through the infusion path underwent standard animal biocompatibility qualification testing including: intramuscular implant test, pyrogen testing and biological test for plastics (USP Class V - modified).

The results indicated that all SynchroMed™ Infusion System materials that directly or indirectly contact body tissue are biocompatible, nonpyrogenic, and nontoxic.

Vascular Catheter Testing

The Model 8500 Access Port and Models 8700, 8702 and 8710 catheters have been commercially available since November, 1985. For the PMA application, the vascular catheters were tested using a vascular catheter along with an Access Port to assess acute and chronic function.

1. Venous Application

Acute venous application studies were performed to assess the surgical and functional techniques required for the implant and use of an access port and indwelling catheter. The surgical placement of the catheters and access ports were achieved in each of two dogs without complication. The access ports were easily located in the subcutaneous tissue by palpation.

The access ports were punctured a total of 116 times over a minimum period of eight weeks for injection or blood withdrawal, and all catheters were patent at termination. The veterinary pathologist reported that gross and histopathologic response were minimal to mild and consistent with chronic cardiovascular catheterizations.

Chronic venous thrombogenicity of a Medtronic Catheter, Model 8702, was assessed relative to that produced by a commercially available vascular catheter by an external laboratory. The catheters were exposed to venous circulation for 30 days. During necropsy, both types of vascular catheters were examined in situ for internal vascular lesions, the presence of thrombi, and the presence of emboli in the heart and lungs. Thrombogenic response and embolus production presented no statistical differences between the two types of catheters.

2. Arterial Application

An acute arterial thrombogenicity evaluation was conducted by an external laboratory. The relative thrombogenicity of a Medtronic Catheter, Model 8702, was compared to a commercially available vascular catheter. Multiple replications of each type of catheter were performed with a replication of positive and negative control materials having known thrombogenic performance during this procedure. Control materials provided procedural validation of the experimental model. After 30 minutes, 12 test catheters and six control materials were observed. Statistical methods demonstrated no significant difference between both types of catheters.

Chronic SynchroMed™ Infusion System Testing

Animal testing was conducted to assess the SynchroMed™ Infusion System performance when used for intravascular chemotherapy. The purpose of these animal studies was to: develop the techniques required for surgical placement, refill and programming; verify biocompatibility; assess SynchroMed™ Infusion System performance during the delivery of the drugs indicated for use; and evaluate component performance in vivo prior to the initiation of human clinical trials.

SynchroMed™ Infusion Systems were implanted in 14 dogs for a total of more than 94 months to infuse FUDR, Adriamycin, heparin or saline. FUDR was delivered intravenously or via the hepatic artery. Adriamycin was delivered into the descending aorta. Heparin was delivered into the inferior vena cava and saline was delivered subcutaneously. The devices were filled with clinically significant concentrations of the indicated drugs, programmed for continuous delivery and monitored. Small drug samples were removed from each of the 14 device reservoirs biweekly for drug stability testing. Sufficient volumes of drugs remained in the reservoirs for continued drug delivery.

At study termination the dogs were sacrificed. The Infusion System was carefully inspected in situ and histopathology was performed on select tissues and all lesions. During the implants, surgical procedures for the components of the device were identified and refined. The programming and refill procedures were developed and the feasibility of external programming was confirmed. As a result of this experience, various modifications were incorporated into the design of the SynchroMed™ pump, catheters and/or programmer. In addition, visual examination of the systems at necropsy and subsequent histopathology verified the biocompatibility of the system materials. The devices demonstrated a volumetric delivery accuracy of $\pm$ 25%.

The animal studies demonstrated that an electromechanical device could be implanted and programmed to deliver pharmaceutical agents directly to a specific site. Procedures for implant and use were documented.

In Vivo Drug Stability

SynchroMed™ Infusion Systems were implanted and monitored for drug stability. The SynchroMed pumps were programmed for continuous delivery and filled as needed with either FUDR, Adriamycin, or heparin. Aliquots of drug were removed from the device reservoirs and analyzed for stability using UV-VIS spectrophotometry and high performance liquid chromatography. Samples were withdrawn weekly, biweekly or monthly to assess stability. Sufficient volumes of drugs remained in the reservoirs for drug stability studies.

The FUDR in vivo stability data verified the in vitro study results in that greater than 90% of the original drug composition was retained following 26 days of reservoir residence. Similarly, the Adriamycin in vivo stability data indicate that greater than 90% of the original drug composition was retained following 14 days of reservoir residence. The FUDR and Adriamycin degradation products observed following device exposure are similar to those produced during normal product shelf life. The heparin in vivo stability data indicate that greater than 90% of the original drug composition is retained following 14 days of reservoir residence and maintains adequate stability for the nontherapeutic intended use.

C. Clinical Studies

A clinical evaluation of the Medtronic SynchroMed™ Infusion System was performed to demonstrate its safety and effectiveness for infusion of cancer chemotherapy drugs and other fluids. The clinical study was intended to examine the performance of the SynchroMed™ Infusion System, rather than the efficacy of the drug therapy. The mode of drug delivery with the SynchroMed™ Infusion System is similar to currently recognized methods. Although the drug labeling guides the physician with respect to drug dosage and infusion sites, the physician may deem it necessary to vary the regimen regardless of the method of infusion. The Medtronic SynchroMed™ Infusion System cancer chemotherapy clinical trial was conducted with FUDR, Adriamycin, and vinblastine. A single device protocol for each drug was followed by all investigational centers. However, investigational centers utilized similar, but not identical, drug therapy protocols. Vinblastine was included in this clinical study as a therapy for renal cell carcinoma and as an alternative to Adriamycin chemotherapy. Although the applicant does not request approval for vinblastine infusion, the device data are relevant to the evaluation of SynchroMed™ pump performance.

Description of Patient Population

One hundred sixty patients were enrolled in the study at seven investigational centers between July 1, 1984 and February 1, 1987. Ninety patients received FUDR, 44 received Adriamycin and 26 received vinblastine. Eight subjects received more than one device in the early phases of clinical studies because of complications. Initial devices were explanted and replaced in six patients. Two patients receiving hepatic FUDR infusions were implanted with two devices simultaneously when the entire liver could not be perfused by cannulating a single artery.

Eighty-six males and 74 females were enrolled in the study. The average patient age was 57.8 years with a standard deviation (SD) of 12.8 years. In general, most patients were refractory to prior surgery, radiotherapy or chemotherapy.

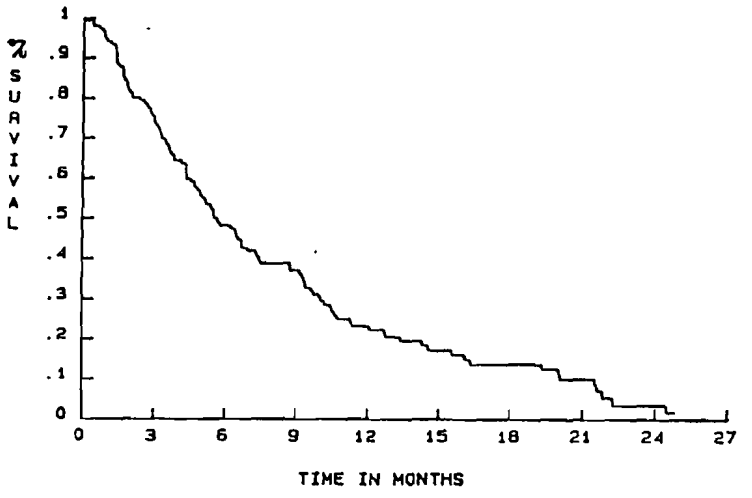
System Experience

One hundred sixty-eight SynchroMed™ Infusion Systems were implanted at seven investigational centers between July 1, 1984 and February 1, 1987, for a total of 1,111 months. The average system follow-up (6.6 months) exceeds the median patient survival (5.8 months), indicating that the data base is sufficiently large to accurately reflect system experience (Figure 1).

The devices were refilled 1,957 times. The devices were programmed 2,029 times and more than 8,100 telemetry transmissions occurred. An average of 127.8 ml of drug was dispensed per device.

The frequency of patient follow up was based upon the pump refill requirements of each patient's therapy. Device accuracy was monitored during the exchange of reservoir fluid volume.

FIGURE 1. SynchroMed™ Infusion System Experience: February 1, 1987



The average system delivery error, excluding the first delivery cycle, is -2.4% (S.D. = 21.6%) indicating a slight underinfusion. System delivery includes complications related to other system components (e.g., catheter) and human error or judgment. The underinfusion is to be expected because most complications that affect fluid delivery inhibit flow. The pump accuracy was assessed following exclusion of delivery errors caused by other system components or procedure related errors that inhibited fluid delivery. The average pump delivery error is +2.2% (S.D. = 10.9%), indicating a slight overinfusion. Measurement error is the largest contributor to the overall variation of delivery error.

A total of 1,111 patient months of catheter experience with 176 implanted catheters was obtained. The average duration of catheter follow-up was 6.3

months (S.D. = 4.1 months).

A total of 667 patient months of access port experience with 130 Access Ports and Port Connector Assemblies was obtained. The average duration of Access Port follow-up was 5.1 months.

SynchroMed™ Pump Reliability

Analysis of the clinical data indicate that the SynchroMed™ Pump is safe and reliable. To assess system reliability, the complications have been categorized as patient, procedure or system related (Figure 2).

FIGURE 2. Complication Overview

Patient Related Complications

A total of 68 complications has been reported. Fifteen were patient related complications. A patient related complication is defined as a complication which is inherent to the disease or the drug being delivered. The patient related complications included pocket infections (concurrent with myelosuppression), vascular occlusions and vascular anomalies. The type and rate of patient related complications reported during this study are not considered extraordinary as indicated in the Table 5 references.

Procedure Related Complications

There was a total of 15 procedure related complications reported (Table 1). A procedure related complication is defined as a complication directly related to the implant procedure or the refill procedure. There were three refill errors (0.1% per refill) and twelve surgical errors (7.1% per surgery).

The complication rate associated with the refill procedure is not considered extraordinary. Examination of the types of surgical errors reported (Table 1) reveals that these complications are preventable. Procedural complications, while not unique to this device, have been addressed through improvements in the Instructions for Use labeling and the implementation of a

precise training and education program.

TABLE 1. Procedure Related Complications

Surgical Complications	Number of Occurrences
Undersized Pocket	1
Catheter Lacerated	1
Catheter Ligated	1
SynchroMed™ Pump Implanted Septum Down	2
Failure to Use Anchoring Rings	5
Failure to Remove Protective Cover from Access Port	1
Catheter Improperly Connected	1
TOTAL SURGICAL COMPLICATIONS	12
Refill Complications	
Microextravasation	1
Extravasation	1
Needle Puncture	1
TOTAL REFILL COMPLICATIONS	3

System Related Complications

There was a total of 38 system related complications (3.4% per month) reported during this clinical trial. Of the 38 system complications, 23 were catheter related complications and 15 were related to other components of the system (pump, port connector, access port, programmer).

Table 2 shows the system complications and the applicant's response to those complications.

TABLE 2. SUMMARY SYSTEM COMPLICATIONS

COMPONENT	COMPLICATION	NO.	TIME TO COMPLICATION (MO.)[a]	RESPONSE
SynchroMed™ Pump	Gear failure	2	0.7,21.8	Mfg. change
	Weld failure	1	1.9	Design change
	Reed Switch failure	1	10.4	None
Access Port	Migration	2	2.6,8.0	Procedure
	Occlusion	1	3.3	Mfg. change
	Leakage	1	4.6	Mfg. change
Port Connector	Kink, Occlusion		2.4,2.7	
	Separation	6	3.0,3.5	
			3.0,11.7	Design change
Programmer	Telemetry Data Error	1	0.0	Design change
Catheter	Partial Occlusion	13	1.6,3.0	Procedure
			3.2,3.7	
			3.8,5.0	
			7.7,9.3	
			11.5,11.7	
			12.5,16.5	
			17.1	
	Occlusion	8	3.2,3.6	Procedure
			3.6,4.8	
			4.8,9.7	
			10.0,14.5	
	Migration	2	0.9,1.4	Procedure
TOTAL		38		

[a] Number of months elapsed post implant

NonCatheter Related Infusion System Complications

Components of the Infusion System have been modified over the course of the clinical trial to reflect the knowledge and experience obtained during the

study. As a result, these design versions have been tested during this study. A summary of the SynchroMed™ Infusion System design changes incorporated in each version and the rationale for those changes is shown in Table 3. The clinical experience obtained for each design version is shown in Table 4.

TABLE 3. Summary of SynchroMed™ Infusion System Design Changes and Rationale

VERSION NO.	COMPONENT	DESIGN CHANGES	RATIONALE
Zero	N/A	Original design	N/A
One	SynchroMed™ Pump	Modified peristaltic pump	Reduce torque load.
		Modified motor	Increase available torque.
		Modified pump tube geometry	Improves delivery characteristics. Reduces spurt.
		Reed Switch	Improve electronic security. Protection from EMI.
		Conformal parylene coating	Protect electronic circuitry in the event of a drug leak.
	Programmer	Programmer software and hardware modified	Software modified to monitor EMI. Magnet added to the programming wand.
	Refill Relief Valve	Model 8692 refill relief valve	Prevent overpressurization during refill. Prevents damage to pump tube.
Two	SynchroMed™ Pump	Hermetic containment of the circuitry	Replaces parylene coating. Improves moisture barrier.
Three	Port Connector	Reduced tubing length	Improved kink resistance. Uniform implant procedure.
		Modified flow characteristics	Improved flush characteristics. Eliminates port connector occlusions.

VERSION NO.	COMPONENT	DESIGN CHANGES	RATIONALE
	Programmer[a]	Modified operating software	Automatic verification of Random Access Memory (RAM). Eliminates telemetry data errors.

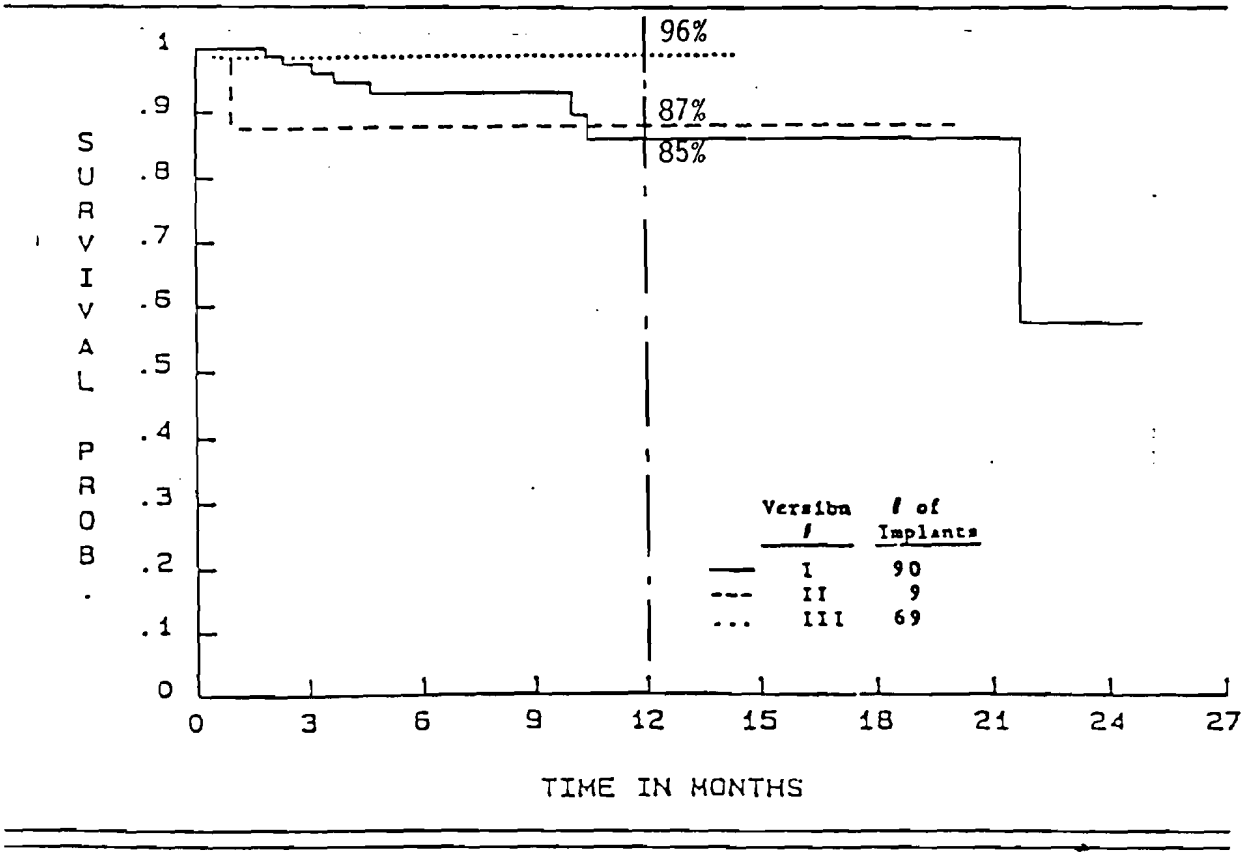
[a] The change was implemented in the operating software of the programmer only. The programmer software change had no effect on the performance of the implanted components.

TABLE 4. Clinical Experience by Design Version

	EXPERIENCE		
DESIGN VERSION	NO. OF IMPLANTS	NO. OF MONTHS	AVERAGE (MONTHS)
I	90	706	7.8
II	09	59	6.6
III	69	346	5.0

Figure 3 shows the probability of freedom from system complications by Design Version. Fourteen of 15 non-catheter related system complications occurred in Design Version I. As design modifications were implemented, system reliability has improved. The probability that an implanted system would not exhibit a complication in the first 12 months was 85% for Version I, 87% for Version II and 96% for Version III.

FIGURE 3. FREEDOM FROM SYSTEM COMPLICATIONS



Catheter Related System Complications

Catheter occlusions and migrations are an inherent risk associated with chronic indwelling catheters. A review of the literature indicates that catheter occlusions can be expected to occur at a rate of approximately 1.1% per month and catheter migrations at a rate of 0.4% per month. The expected commercial catheter complication rates are based upon over 2600 months of

clinical experience reported in nine literature references (Table 5). Included in the nine references are three implantable pump papers, three external catheter papers, and three implantable access port papers.

In this clinical trial, irreversible catheter occlusions occurred at a rate of 0.7% per month and catheter migrations a rate of 0.2% per month. The incidence of catheter complications in this study is not statistically significantly different from the expected rate reported in the literature.

TABLE 5. COMPARISON-OF VASCULAR CATHETER PERFORMANCE

COMPLICATION TYPE	MEDTRONIC RATE (% PER MONTH)		AVERAGE COMMERCIAL RATE (% PER MONTH)[a]
Catheter Occlusion	0.7	p = 0.211	1.1
Catheter Migration	0.2	p = 0.524	0.4

a Literature References:

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2. Bothe, A., W. Piccione, J.J. Ambrosino, P.N. Bennotti, and J.J. Lokich. "Implantable Central Venous Access System". American Journal of Surgery. 147:565-569. 1984.

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6. Niederhuber, J.E., W. Ensminger, J.W. Gyves, M. Liepman, K. Doan, and

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7. Reilly, J.J., D.L. Steed, and P.S. Ritter. "Indwelling Venous Access Catheters in Patients with Acute Leukemia". Cancer. 53:219-223. 1983.

8. Stoppenbach, M., Unpublished data, personal communication. 1985.

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Potential Complications

The preceding discussion has demonstrated that noncatheter related system complications have been corrected through the implementation of design modifications and manufacturing process changes. In addition, it has been shown that the incidence of catheter complications reported in this study is not significantly different from the expected rate reported in the literature.

As a result, the potential complications related to the use of this device include, but may not be limited to, the following (Table 6): cessation of therapy due to battery depletion or random component failure; pocket seroma; hematoma; erosion or infection; migration of the access port; rupture of the connector assembly at high injection pressures; complete and partial catheter occlusions; catheter migration; and drug toxicity and related side effects.

TABLE 6. Potential Complications

COMPONENT	COMPLICATION	RATE % PER DEVICE	RATE % PER MONTH
SynchroMed™ Pump	Cessation of therapy due to battery depletion or random component failure[b]	NA[a]	NA
	Pocket Erosion or Infection	0.6	0.1
Access Port	Migration	1.5	0.3
Catheter	Reversible Occlusion	7.7	1.2

	Irreversible Occlusion	4.8	0.7
	Migration	1.2	0.2
Drug Toxicity	See Drug Label	NA	NA

[a] Denotes Not Applicable or random occurrence.

[b] Battery testing indicates the power source will function for 3 years at a flow rate of 1.5 ml/day.

VII. CONCLUSIONS DRAWN FROM THE STUDIES

Since July of 1984, 168 SynchroMed™ Infusion Systems have been implanted for over 1,100 months. The average patient follow-up is 6.6 months, and 27 devices have been implanted and functioning for over 12 months. The SynchroMed™ implantable pump has demonstrated its programmability via telemetric control to allow noninvasive dose adjustment and claimed accuracy in fluid delivery.

The information presented in the Premarket Approval Application is valid scientific data which support the safety and effectiveness of the system. The laboratory tests substantiate the specifications of the device, provide evidence of its claimed life expectancy, and demonstrate the capability to perform as expected in varying environmental conditions that patients may encounter. The animal test results demonstrate that the device is biocompatible, nonpyrogenic, and nontoxic. The results of the clinical studies indicate that the device is safe and effective for the stated indications for use and does not present unreasonable risk when used under conditions of intended use and in accordance with the final draft labeling.

The results of the laboratory, animal, and clinical studies conducted using the Medtronic SynchroMed™ Infusion System provide the requisite assurance of the safety and effectiveness of the device for the stated indications.

VIII. PANEL RECOMMENDATION

The General Hospital and Personal Use Devices Panel met on November 3, 1986, to consider the safety and effectiveness of the SynchroMed™ Infusion System. The Panel recommended that CDRH approve the PMA for the SynchroMed™ Infusion System subject to providing data on 20 - 30 patients implanted with the device for 1 year or longer, revise the physician's and patient's manuals to include pertinent information learned during the clinical trials, provide a 24 hour telephone back-up service for physicians and patients, and include all possible complications and the rates of occurrence in the device labeling.

IX. CDRH DECISION

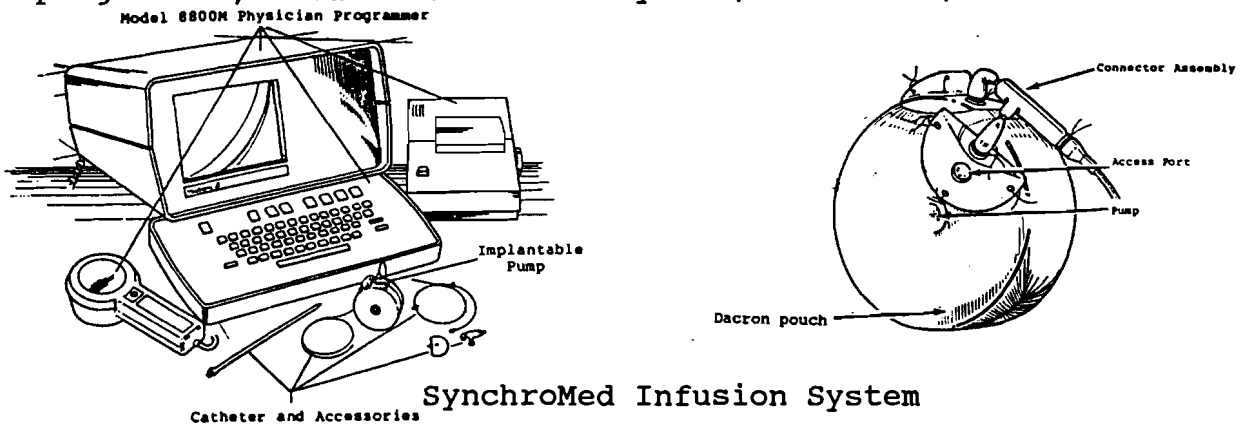
CDRH concurs with the recommendation of the General Hospital and Personal Use Devices Panel and believes that the benefits of the device outweigh its risks, and that there is reasonable assurance that the device is safe and effective for its stated indication. An approvable letter dated July 23, 1987, was sent to the applicant requesting that the labeling be revised to include the life expectancy of the SynchroMed™ Infusion System based on the clinical experience to date, the anticipated rate of each complication, instructions for the physicians during periods of nontherapy, a justification for the SynchroMed™ Infusion System that has no bacterial filter, justification that all five delivery modes should be considered approvable, and concurrence with the conditions that the SynchroMed™ Infusion System be restricted to prescription use, that the device is restricted insofar as the approved labeling specifies the requirements that apply to the training of physicians who may use the device, the conduction of a postapproval study and submission of reports to FDA on clinical experience gained with the first five patients followed for 3 months at each of 10 new medical centers, and postapproval reports and all annual reports must include a summarization of all expected and unexpected adverse effects. On August 4, 1987, the applicant submitted an amendment to CDRH which satisfactorily supplied the requested information. CDRH issued an approval order for the stated indications for the applicant's PMA for the Medtronic Inc. SynchroMed™ Infusion System on MAR 14 1988. An inspection of the applicant's manufacturing facility found it to be in compliance with the Good Manufacturing Practices (GMP) Regulation.

X. APPROVAL SPECIFICATIONS

The approval specifications are shown in the approval letter (Attachment B). The final printed labeling and all subsequent changes in the labeling may be viewed at the Food and Drug Administration, Center for Devices and Radiological Health, Office of Device Evaluation, 8757 Georgia Avenue, Silver Spring, Maryland 20910.

PREFACE
SynchroMed Infusion System

The Medtronic SynchroMed Infusion System includes a programmable pump, a programmer, a catheter access system, catheters, and accessories.



SynchroMed Infusion System

The system is designed to contain and to administer parenteral drugs to a specific site. The implantable devices include the pump, catheter access system, catheters, and accessories. The external part of the system is the SynchroMed Model 8800M Physician Programmer, which is used to noninvasively program and interrogate the implanted pump.

INDICATIONS

The SynchroMed Infusion System is indicated for use when patient therapy requires the chronic intravascular infusion of floxuridine or doxorubicin. In addition, the nontherapeutic use of bacteriostatic water, physiological saline, and/or heparin is indicated when necessary to support this mode of cancer therapy.

The regional intra-arterial infusion of floxuridine is used in the palliative management of unresectable solid colorectal tumors metastatic to the liver.

The systemic intravenous infusion of doxorubicin is used in the palliative management of various solid tumors, lymphomas, and leukemias.

Bacteriostatic water or physiological saline can be used to achieve the physician-prescribed concentration of floxuridine or doxorubicin and to flush the pump reservoir. Heparinized physiological saline may be used during an interruption in floxuridine therapy to maintain catheter patency.

Physicians prescribing the SynchroMed Infusion System for use with floxuridine or doxorubicin must be familiar with the indications, contraindications, and warnings described in the drug labeling. Except under approved conditions of Investigational Device Exemptions, the use of the SynchroMed Infusion System is restricted to the infusion of the drugs and fluids previously described.

CONTRAINDICATIONS

The device should not be implanted in the presence of infection.

Implantation is contraindicated when the pump cannot be implanted less than 2.5 cm (one inch) from the surface of the skin and/or when the patient has an implanted programmable medical device.

Patients whose body size is not sufficient to accept the pump bulk and weight are not suitable candidates.

Contraindications relating to the use of the prescribed drug should be observed.

SYSTEM DESCRIPTIONS

For a complete description of components, indications, contraindications, warnings, and precautions please refer to the appropriate sections of each component manual.

Programmable Pumps

SynchroMed Models 8610H and 8611H Programmable Pumps are implantable, battery-powered devices that store and dispense drugs according to instructions received from the SynchroMed Programmer.

Both pumps contain a collapsible 18 ml drug reservoir, microprocessor-based circuitry, lithium thionyl-chloride battery, antenna, acoustic transducer, peristaltic pump, and fill port with a self-sealing septum and a needle stop. Model 8611H also contains a bacterial retentive filter through which the drug passes as it leaves the drug reservoir. A Dacron pouch included in the pump package serves to fix the pump in the subcutaneous pocket as well as to anchor the optional catheter access port.

Examine the shipping package carefully. If the package is damaged or the "Use Before..." date is past, do not implant or resterilize the pump. Return the pump and its shipping package to Medtronic, Inc.

To assure SynchroMed pump accuracy: limit the reservoir fill volume at implant to 10 ml and subsequent refill volumes to 18 ml. Program the pump to deliver not less than 0.6 ml/day (0.025 ml/hour).

The following programmable modes have not been used in cancer chemotherapy clinical studies: bolus, multistep bolus, and bolus delay. These modes are not recommended for vascular applications due to the intermittent periods of no flow and the possible increased risk of catheter occlusion.

Vascular Catheters

SynchroMed Vascular Catheters are totally implantable devices designed to provide a fluid pathway for drug administration and/or diagnostic procedures. The catheter body is constructed of radiopaque materials and incorporates a strain-relief connector assembly for attachment to a SynchroMed Programmable Pump or Medtronic Catheter Access Port.

The Model 8700 Vascular Catheter is designed for general intravascular use and may be trimmed to desired length. Fixation rings are attached to the distal portion. The catheter comes packaged with a guidewire, anchoring sleeves, and plastic tips for a metal tunneling rod (supplied separately).

The Model 8702 Vascular Catheter is designed specifically for intra-arterial, small vessel access, and may be trimmed to facilitate introduction. Fixation rings are attached to the distal portion. The catheter is packaged with anchoring sleeves and plastic tips for a metal tunneling rod (supplied separately).

The Model 8710 Vascular Catheter is designed for intravenous use and can not be trimmed to length because of its trilaminate construction (a small inner silicone tubing, a high-strength metal coil, and a large outer silicone tubing). Therefore, the Model 8710 is provided in two lengths. It is packaged with anchoring sleeves and plastic tips for a metal tunneling rod (supplied separately).

Catheter occlusions may inhibit drug delivery. Refer to the vascular catheters technical manual for details on methods of clearing an occluded catheter.

To maintain catheter patency during periods of nontherapy, the pump should be emptied of drug and filled with saline (or an appropriate heparinized solution) and programmed to a continuous flow rate of not less than 0.6 ml/day. Do not stop the pump during periods of nontherapy.

Catheter Access System

The SynchroMed Model 8500-1 Catheter Access System provides a transcutaneous entry point, via syringe, to an implanted SynchroMed Catheter for drug administration and/or diagnostic purposes. The system allows a catheter to be attached to both a SynchroMed Pump and an access port.

The access port housing is a molded biocompatible thermoplastic and contains a self-sealing septum, needle stop, infusion pathway, three suture points, and a titanium catheter port. The connector assembly is a T-shaped connector consisting of two silicone connectors, a titanium catheter port, and an in-line valve.

The catheter access system is not intended for use in blood withdrawal.

If the presence of blood is suspected in the catheter access system, flush the system with a minimum of 10 ml of saline (a heparinized solution may be used if not contraindicated).

Programmer

The SynchroMed Model 8800M Physician Programmer is designed for use by the clinician to noninvasively program and interrogate an implanted SynchroMed Programmable Pump. The programmer establishes a two-way, radio-frequency (RF) link with the implanted pump to transmit interrogation and programming signals to the pump and to receive status information from the pump. The programmer is a line-powered, desk top device consisting of a console, keyboard, programming wand, and a printer.

The Model 8800M Physician Programmer should be used only for programming Medtronic SynchroMed Programmable Pumps. The programmer operates best in an environment which is free from strong electromagnetic interference.

TECHNICAL SUPPORT

A toll-free technical support service is available 24 hours a day for clinicians managing SynchroMed Infusion System implants: Telephone Customer Service at : 1-800-328-0810.